REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-2, 4-5, 7-18 and 20-21 are pending with entry of this amendment, claims 3, 6 and 19 being cancelled herein and claims 22-23 being cancelled in a previous amendment. Claim 1 is amended herein. The amendment introduces no new matter and support is replete throughout the specification. The amendment is made without prejudice and should not be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 1, support for the amendments can be found throughout the specification. For example, support for the biochip can be found at paragraphs 0041-0045, 0090-0091, and the Figures; support for polyclonal antibody affinity reagents can be found, for example, at paragraphs 0010, 0071-0074 and original claim 3; support for analyzing the mass spectrum data comprising molecular masses of the captured protein can be found, for example, at paragraphs 0079-0086, 0088-0091 and 0098-0114. Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §102.

The rejection of claims 1-6, 10-12, 15 and 19-21 as allegedly anticipated under 35 U.S.C. §102(e) by Monforte (USPN 7,091,046) was maintained by the Office. Applicants traverse.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Claims 1-6, 10-12, 15 and 19 are drawn to methods for determining the presence of host cell proteins in a sample, including the steps of (a) capturing host cell proteins from a sample onto a biochip having a solid support comprising a mixture of biospecific affinity reagents bound to the solid support and comprising a mixture of polyclonal antibodies that specifically bind host cell proteins of a particular host organism; (b) detecting the captured proteins by mass spectrometry to produce a mass spectrum comprising molecular masses of the captured proteins or ionized fragments thereof; and (c), analyzing the mass spectrum, thereby determining the presence of the host cell protein contaminants in the sample. Claims 20-21 are drawn to methods of following purification of a target protein involving profiling samples using the methods of claim 1.

Monforte is alleged to teach or describe multiplexed assays for determining protein levels within a sample. The Monforte assays employ a biodisplayed polypeptide binding component

(a phage-display antibody) that contains a predetermined marker sequence (an expression cassette encoding the Monforte "signature polypeptide"); the bio-displayed polypeptide binding component is used to bind to the protein of interest, then the predetermined marker component is amplified and the signature polypeptide detected (see Monforte abstract and column 2, lines 44-50).

However, the Monforte publication does not teach all of the limitations of the claimed invention. For example, Monforte does not teach or disclose using affinity reagents comprising a mixture of polyclonal antibodies that specifically bind to proteins from a particular host organism (e.g., host organism-specific affinity reagents). Nor does Monforte teach or disclose detecting the molecular masses *of the captured proteins* by mass spectrometry. As noted herein, the Monforte assays detect a surrogate molecule -- the signature marker polypeptide -- and not the captured protein itself. Per column 14, lines 1-6 of the Monforte publication, "In embodiments herein the signature polypeptide is detected and quantitated by mass spectrometry" (emphasis added). Because the cited art does not teach every element of the claimed invention, Applicants submit that the rejection is improper and respectfully request that it be withdrawn.

35 U.S.C. §103(a).

CLAIMS 7-9 ARE PATENTABLE OVER MONFORTE AND HUTCHENS

Claims 7-9 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Monforte (USPN 7 091,046) in view of Hutchens et al. (US 2001/0014461). Applicants traverse.

Criteria for obviousness

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P. § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. §2143. Applicants submit that the claims are patentable over Monforte in view of Hutchens, because the cited publications do not meet these criteria.

Claims 7-9 are drawn to methods for determining the presence of host cell proteins in a sample using a surface enhanced laser desorption/ionization (SELDI) biochip. The methods include the steps of a) capturing host cell proteins from a sample onto a SELDI biochip having a solid support comprising a mixture of biospecific affinity reagents bound to the solid support and comprising a mixture of polyclonal antibodies that specifically bind host cell proteins of a particular host organism,

wherein the mixture of biospecific affinity reagents is immobilized before or after capturing the host cell proteins; b) detecting the captured proteins by mass spectrometry to produce a mass spectrum comprising molecular masses of the captured proteins or ionized fragments thereof; and c) analyzing the mass spectrum, thereby determining the presence of the captured host cell protein contaminants in the sample

Monforte is alleged to teach multiplexed assays for determining protein levels within a sample using MALDI-based methods, but not the use of SELDI. Hutchens is alleged to disclose the advantages of SELDI over MALDI. However, the publications (alone or in combination) do not meet the criteria for proving a *prima facie* case of obviousness.

The limitations of the claimed invention are not taught by the cited art

First, the cited publications do not teach all of the limitations of the claimed invention. The Office alleges that "Monforte further discloses a binding moiety such as an antibody attached to a solid support that captures the target protein and a second binding moiety containing a signal generating element then binds to the captured target protein (column 13, lines 55-65). The protein is then detected and quantitated (column 14, lines 1-8)." Applicants respectfully submit that this representation is inaccurate. The latter passage cited from Monforte actually states:

> In the methods provided herein, the signal-generating element is a genetic package, such as a bacteriophage, that can infect and multiply within a host (the amplification component) and also code for the expression of a unique signature polypeptide (the detectable signal component) that is subsequently detected. In embodiments herein **the signature polypeptide is detected and quantitated** by mass spectrometry.

(emphasis added). Thus, Monforte does not teach detection of the captured protein itself, but rather a surrogate molecule (the signature marker polypeptide) that has been produced and then detected (also see, for example, column 27, lines 20-52; and the abstract). Application of the SELDI techniques taught by Hutchens to the methods of Monforte does not change the fact that Monforte does not teach producing a mass spectrum comprising molecular masses of the captured proteins.

Furthermore, Monforte does not teach or describe mixtures of biospecific affinity reagents bound to a solid support and comprising a mixture of polyclonal antibodies that specifically bind a plurality of host cell proteins of a particular host organism, and the Office has not indicated how Hutchens remedies this deficit.. Since Monforte and Hutchens, alone or in combination, do not teach all of the limitations of the claimed invention, the first criterion for proving a *prima facie* case of obviousness has not been met.

There is no motivation provided to modify the Monforte methods

The Office has alleged that the motivation to adapt the Monforte methods to use the SELDI and SEND detection methods taught in Hutchens is better specificity, selectivity and sensitivity. However, as noted above, Monforte does not detect or analyze signals from the captured polypeptide itself. Monforte in essence provides an improved sandwich-type ELISA assay involving generation and detection of a secondary signal detection component (the "signature polypeptide"), the coding sequence for which is carried within the phage display library member displaying the second antibody of the ELISA "sandwich." In the Monforte methods, after binding of the target protein, the nucleic acid sequence encoding the signature polypeptide is retrieved from the phage, amplified, and the expressed peptide detected, e.g., by mass spectrometry (column 2, lines 40-52; column 14, lines 1-15; column 27, lines 11-19; and column 31, lines 28-39).

Detection of the Monforte "signature polypeptide" is essential to the methods taught in the publication, and the advantages of such an approach over alternative (direct) detection strategies are cited throughout the Monforte publication; see, for example, column 14 lines 9-15 and column 16 lines 17-23. Furthermore, the Monforte methods are directed to overcoming limitations of ELISA and various direct visualization technologies, and thus teaches away from detection techniques such as those of the claimed invention (column 1, line 59 through column 2, line 36). There is no motivation for one of skill in the art to modify the Monforte detection methods in a manner that removes the use of the (essential) Monforte signal polypeptide.

Nor does Hutchens provide the motivation necessary to modify the Monforte methods to produce the claimed invention. Hutchens is only alleged to teach the advantages of SELDI over MALDI; the publication does not provide any motivation to modify the Monforte methods such that the Monforte signal polypeptide (essential to the cited advantages of performing the Monforte methods as compared to alternative detection methods) is no longer utilized. Furthermore, there is no motivation provided in either publication for one of skill in the art to perform the Monforte ELISA-style sandwich interaction in the presence of a SELDI matrix, given that the Monforte signal polypeptide must subsequently be generated (via retrieval of the expression cassette and expression of the encoded signal polypeptide). In light of the teachings of Monforte, Applicants respectfully submit that the cited publications do not meet the second criterion for proving a *prima facie* case of obviousness.

No reasonable expectation of success has been provided

Third, a reasonable expectation of successfully producing the claimed invention is required for proving a *prima facie* case of obviousness. As noted above, the Monforte methods

involve detection of a "signature polypeptide" generated from the detectable signal component that was incorporated into the captured phage display library member (see Figure 1). The Office has alleged that one of skill would apply a layer of energy absorbing material (matrix material) as provided by Hutchens "onto which the analyte (the target proteins of Monforte) is placed" and then "cause the analyte to be desorbed" (page 5 of the Action mailed April 17, 2008). However, one of skill in the art and intending to practice the Monforte methods would readily recognize that the Monforte methods cannot be successfully practiced absent generation of the Monforte "signature polypeptide," which one of skill would not expect to successfully produce having applied the target protein to an energy-absorbing matrix per the steps described by the Office. Furthermore, even if one of skill in the art were to apply the Hutchens SELDI techniques to the assay methods taught by Monforte, one would not produce a mass spectrum comprising molecular masses of the captured proteins (or ionized fragments thereof), since what is being detected using the Monforte methods is the "signature polypeptide" (i.e., a surrogate for the captured protein). Thus, there is no reasonable expectation of successfully producing the methods of the claimed invention based upon the teachings of the cited art. Applicants respectfully submit that, since the cited publications, alone or in combination, do not provide a reasonable expectation of success, the third criterion for proving a *prima facie* case of obviousness has not been met.

Summary

Since Monforte and Hutchens, alone or in combination, do not meet the criteria for proving a *prima facie* case for obviousness (all of the claimed elements are not taught, there is no motivation to modify the cited art, nor is there a reasonable expectation of successfully producing the claimed invention), Applicants submit that the claims are patentable over the cited art and respectfully request that the rejection be withdrawn.

CLAIMS 13 AND 14 ARE PATENTABLE OVER MONFORTE AND SCHWARTZ

Claims 13 and 14 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Monforte in view of Schwartz (2006 J. Mol. Recog. 9:672-674). Applicants traverse.

As noted above, a *prima facie* case of obviousness requires that the cited art, alone or in combination, must provide all of the elements of the claimed invention, a teaching, suggestion or motivation to combine the references, and an expectation of successfully producing the claimed invention. Claims 13 and 14 are drawn to methods of determining the presence of host cell proteins using a solid support comprising a chromatographic resin derivatized with the capture molecules, which members may include Protein A, Protein G, and mercaptoheterocyclic ligands. Monforte is

alleged to teach antibodies attached to solid supports, such as chromatographic resins; Schwartz is alleged to teach mercaptoheterocyclic ligands that specifically bind antibodies. However, the cited art, alone or in combination, does not meet the criteria for obviousness.

First, the cited publications do not teach all of the limitations of the claimed invention. As noted above, Monforte does not teach or disclose the claimed polyclonal antibodies bound to the solid support, or the step of detecting the captured proteins by mass spectrometry to produce a mass spectrum comprising molecular masses of the captured proteins or ionized fragments thereof. Application of the mercaptoheterocycle adsorption ligands taught by Scwartz to the methods of Monforte (i.e., as a means for coupling the Monforte antibodies to the solid substrate) does not remedy the deficits in the Monforte teachings. Furthermore, there is no motivation in either Monforte or Schwartz to omit the critical Monforte step with respect to the signal detection component (the "signature polypeptide"), or any reasonable expectation of producing the methods of the claimed application in light of the signal detection components essential to the Monforte methods.

Since Monforte and Schwartz, alone or in combination, do not meet the criteria for proving a *prima facie* case for obviousness (all of the claimed elements are not taught, there is no motivation to modify the cited art, nor is there a reasonable expectation of successfully producing the claimed invention), Applicants submit that the claims are patentable over the cited art and respectfully request that the rejection be withdrawn.

CLAIM 16 IS PATENTABLE OVER MONFORTE AND PIASIO

Claim 16 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Monforte (USPN 7 091,046) in view of Piasio (USPN 4,098,876). Applicants traverse.

As noted above, a *prima facie* case of obviousness requires that the cited art, alone or in combination, must provide all of the elements of the claimed invention, a teaching, suggestion or motivation to combine the references, and an expectation of successfully producing the claimed invention. Claim 16 is drawn to methods of determining the presence of host cell proteins using a mixture of biospecific affinity reagents bound to the solid support, in which the host cell proteins are bound to the affinity reagent and the affinity reagent is subsequently captured on the solid support. The captured proteins are then detected by mass spectrometry, thereby producing a mass spectrum comprising the molecular masses of the captured proteins.

Monforte is alleged to teach a step "wherein a binding moiety such as an antibody attached to a solid support captures the target protein and a second binding moiety comprising a second antibody with a signal generating element then binds to the captured target protein (column

13, lines 55-65)"; Piasio is alleged to teach incubating with the "second" (non-immobilized) antibody prior to providing with the immobilized antibody. However, the cited art, alone or in combination, does not meet the criteria for obviousness.

First, the cited publications do not teach all of the limitations of the claimed invention. As noted above, Monforte does not teach or disclose the claimed polyclonal antibodies bound to the solid support, or the step of detecting the captured proteins by mass spectrometry to produce a mass spectrum comprising molecular masses of the captured proteins or ionized fragments thereof. Applying the teachings of Piasio to the methods of Monforte (exposing the target protein to the Monforte phage-displayed antibody prior to the solid-phase Monforte antibody) does not remedy the deficits in the Monforte teachings. In addition, there is no motivation in Monforte or provided by Piasio to omit the critical Monforte step with respect to the signal detection component (the "signature polypeptide"), or any reasonable expectation of producing the methods of the claimed application in light of the signal detection components essential to the Monforte methods.

Since Monforte and Piasio, alone or in combination, do not meet the criteria for proving a *prima facie* case for obviousness (all of the claimed elements are not taught, there is no motivation to modify the cited art, nor is there a reasonable expectation of successfully producing the claimed invention), Applicants submit that the claims are patentable over the cited art and respectfully request that the rejection be withdrawn.

CLAIMS 17 AND 18 ARE PATENTABLE OVER MONFORTE, PIASIO, HUTCHENS AND SCHWARTZ

Claims 17-18 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Monforte (USPN 7 091,046) in view of Piasio in further view of Hutchens et al. (US 2001/0014461) and Schwartz. Applicants traverse.

As noted above, a *prima facie* case of obviousness requires that the cited art, alone or in combination, must provide all of the elements of the claimed invention, a teaching, suggestion or motivation to combine the references, and an expectation of successfully producing the claimed invention. Claims 17 and 18 are drawn to methods of determining the presence of host cell proteins using a mixture of biospecific affinity reagents bound to the solid support, in which the solid support is a SELDI biochip derivatized with a capture molecule that binds to the affinity reagent. The captured proteins are then detected by mass spectrometry to produce a mass spectrum comprising the molecular masses of the captured proteins.

Monforte is alleged to teach antibodies attached to solid supports (column 13, lines 55-65), including chromatographic resins such as glass (column 12, lines 56-65). Hutchens is alleged to disclose the advantages of SELDI over MALDI in terms of specificity, selectivity and sensitivity (paragraph [0188]); Schwartz is alleged to teach mercaptoheterocyclic ligands that readily adsorb antibodies (page 673); Piasio is alleged to teach incubating with the "second" (non-immobilized) antibody prior to providing with the immobilized antibody. However, the cited art, alone or in combination, does not meet the criteria for obviousness.

First, as has been noted above, none of the cited publications teach all of the limitations of the claimed invention. Monforte does not teach or disclose the claimed polyclonal antibodies bound to the solid support, or the step of detecting the captured proteins by mass spectrometry to produce a mass spectrum comprising molecular masses of the captured proteins or ionized fragments thereof. These deficits are not remedied by the additionally cited publications. Applying the teachings of Piasio to the methods of Monforte (i.e., exposing the target protein to the Monforte phage-displayed antibody prior to the solid-phase Monforte antibody), and/or the mercaptoheterocycle adsorption ligands taught by Scwartz (i.e., as a means for coupling the Monforte antibodies to the solid substrate), and/or the matrix materials and SELDI procedures as provided by Hutchens, does not remedy the deficits in the Monforte teachings to produce the claimed invention. Furthermore, as noted in the previous arguments, there is no motivation in any of the cited publications to omit those assay elements/steps (involving the expression cassette "signal generation component" and the subsequently expressed "signature polypepetide") that are essential to the function of the Monforte methods and provide the desired advantages over other detection techniques; see, for example, column 14 lines 9-15 and column 16 lines 17-23. Nor does the Office provide how one of skill in the art would have any reasonable expectation of performing the methods of the claimed application (for example, detecting the captured proteins by mass spectrometry to produce a mass spectrum comprising molecular masses of the captured proteins or ionized fragments thereof) using the surrogate detection components essential to the Monforte methods.

Since Monforte, Piasio, Hutchens and Schwartz, alone or in combination, do not meet the criteria for proving a *prima facie* case for obviousness (all of the claimed elements are not taught, there is no motivation to modify the cited art, nor is there a reasonable expectation of successfully producing the claimed invention), Applicants submit that the claims are patentable over the cited art and respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Respectfully submitted,

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1) A Notice of Appeal;
2) A petition to extend the period of response for **3** months;
3) A transmittal sheet;
4) A fee transmittal sheet; and
5) A receipt indication postcard.